DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 4/2/08 are acknowledged.

2. Claims 1-2, 4-6, 8, 10 and 12-15 were amended.

3. Claims 1-2 and 4-15 are included in the prosecution.

Response to Arguments

Objection to claim 4

4. In light of Applicant's amendment to correct the dependency, the objection to claim 4 is withdrawn.

Rejection of claim 1 under 35 USC § 112

5. In light of Applicant's amendment to claim 1 to replace "said compound" with "said cationic lipid", the rejection under 35 USC § 112, second paragraph is withdrawn.

Rejection of claims 1-2 and 4-15 under 35 USC § 103(a)

6. Applicant's arguments, see Page 10, filed 4/2/08, with respect to the rejection of claims 1-2 and 4-15 under 35 USC § 103(a) as being unpatentable over Kadouche (WO 01/52889) in view of Singh et al. (Cancer Letters 84 (1994) 15-21) have been fully considered but are not persuasive.

Applicant argues (see Page 12) that Kadouche does not teach how to couple the antibody to the carrier (i.e., liposome, emulsion or lipid) of the drug. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). Although Kadouche does not expressly teach cationic lipids selected from the group consisting of a C_{10}-C_{24} alkylamine, a C_{10}-C_{24} alkanolamine and a cholesterol ester and a heterobifunctional linker, the supporting reference, Singh, provides the teaching of using C_{10}-C_{24} alkylamine (stearyl amine or SA) in liposomal preparations along with using a heterobifunctional reagent (SPDP).

Applicant argues (see Page 13) that the teaching by Singh in no way suggests a positive oil-in-water emulsion as recited in claim 1. Applicant submits (see Page 11) that combination of the teachings of Kadouche and of Singh would not have led one skilled in the art, at the time the invention was made, to produce the combination product of claim 1. Applicant argues (see Page 13) that Kadouche or Singh, taken alone or in combination, does not teach, suggest or make obvious a drug delivery system as recited in claim 1 and that combining the teachings of Kadouche and Singh would not yield predictable results.

This is not found persuasive because one with ordinary skill in the art would know that the cationic lipid (SA) taught by Singh can be used in liposomal preparations or in emulsion preparations. One with ordinary skill in the art would find it obvious to try and use lipids that are available (such as SA) in liposomes or in emulsions. Therefore, since Kadouche teaches a monoclonal antibody coupled to a liposome or to a cationic emulsion, and Singh teaches cationic lipids such as SA, one with ordinary skill in the art would find it obvious to try the cationic lipid in liposomes or in cationic emulsions. It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose from a finite number of predictable cationic lipids in liposomal or

emulsion formulations with a reasonable expectation of success of producing a functional product with a cationic type emulsion comprising a cationic lipid linked to an antibody by a heterobifunctional linker.

Applicant argues (see Page 14) that the positive effects on the potentiating ability of a potentiator, which results from encapsulation of the potentiator in antibody targeted liposomes, are not predictive of the effects that such an encapsulation would have on the activity of a drug. Applicant argues that the effects of encapsulations in targeted liposomes on the potentiating ability of a potentiator are even less predictive of the effects of encapsulation in a targeted emulsion on the activity of a drug. Applicant argues (see Page 15) that Singh does not provide any explanation for the observed increase in potentiation, and that Singh is not predictive for using an emulsion type system as in claim 1 of the instant application. Applicant argues (see Page 16) that Singh teaches away from using an emulsion type system and that those skilled in the art, at the time the invention was made, would not have been motivated to combine the teachings of Kadouche and Singh, and even if they were, they would not have been motivated to couple an antibody to an emulsion to develop a targeted drug delivery system given the teaching away in Singh.

This is not found persuasive because although Singh teaches a liposomal preparation, it is used for the teaching of cationic lipids coupled to antibodies using heterobifunctional reagents. The primary reference Kadouche teaches that cationic lipids can be used in cationic type emulsions. One with ordinary skill in the art would find it obvious to use the cationic lipids taught by Singh in the cationic type emulsions of

Kadouche because when a lipophilic substance is dispersed in a hydrophilic substance, an emulsion will form. All the claimed elements (cationic type emulsion, cationic lipid, monoclonal antibody, heterobifunctional linker) are found in Kadouche and Singh and one with ordinary skill in the art could have combined the elements and the combination would have yielded predictable results (a cationic type emulsion with a cationic lipid linked to a monoclonal antibody with a heterobifunctional linker). See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 10/2/07 is maintained.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2 and 4-15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kadouche (WO 01/52889) in view of Singh et al. (Cancer Letters 84 (1994) 15-21).

(The corresponding US patent application publication (US 2002/0106324 A1 is being used as a reference since an English translation of the WIPO document (WO 01/52889) was not available).

The claimed invention is a cationic oil in water emulsion comprising a compound with free NH_2 groups and an antibody and a method for producing the emulsion. The compound is linked to the antibody by a heterobifunctional linker. The emulsion contains an active drug. The antibody (polyclonal or monoclonal) targets antigens.

Kadouche et al. (US 2002/0106324 A1) teaches a monoclonal antibody coupled to a liposome type vector or to cationic type emulsions and also a cationic lipid (Page 5, [0064]). Kadouche teaches native antibodies as immune effectors used in anti-tumoral therapies, which involves "blocking a receptor of the target cell or an anti-idiotypic vaccination for the tumoral antigen" (Page 2, [0018]). Also taught are polyclonal antibodies along with their affinity for ferritins (Page 3, [0047] and Page 4, Table 1). Kadouche teaches an anti-ferritin monoclonal antibody and specifically AMB8LK which was "used to carry out a sandwich ELISA test to detect human ferritins" (Page 7, [0114]).

Kadouche does not expressly teach cationic lipids selected from the group consisting of a C_{10}-C_{24} alkylamine, a C_{10}-C_{24} alkanolamine and a cholesterol ester and a heterobifunctional linker.

Singh teaches monensin liposomes linked to tumor specific monoclonal antibodies with full retention of immunoreactivity (Abstract). Dipalmitoyl phosphatidylcholine (DPPC), cholesterol (CHOL), and stearyl amine (SA) were used in the liposomal preparation (Page 16, left hand column, 2.1). "Immunotoxins against the CEA (anticarcinoembryonic antigen) were produced with these antibodies by conjugating the native ricin A chain to the antibody using the heterobifunctional reagent,

N-succinimidyldithiopropionate (SPDP)" (Page 16, left hand column, 2.2). [^{3}H]Monensin liposomes were prepared with the lipid composition DPPC/CHOL/SA/PDP-SA (5:3:1:1) (Page 16, right hand column, 2.4). The heterobifunctional reagent SPDP was used to introduce pyridyl disulphide groups into the monoclonal antibodies (Mabs) (Page 16, right hand column, 2.5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a product with a monoclonal antibody coupled to a liposome type vector, a cationic type emulsion, or a cationic lipid, as suggested by Kadouche, combine it with the monensin liposomes linked to tumor specific monoclonal antibodies with full retention of immunoreactivity, as suggested by Singh, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Singh discloses that monoclonal antibody targeted monensin liposomes were 100 times more potent than monensin liposomes in potentiating the activity of ricin A immunotoxins against various tumor cell lines in vitro (Abstract). Moreover, since Kadouche teaches that cationic lipids can be used in cationic type emulsions, one with ordinary skill in the art would find it obvious to try the cationic lipid disclosed by Singh in the cationic type emulsion with a reasonable expectation of success.

Regarding instant claim 1, the limitations of a combination product comprising a positively charged oil in water emulsion, cationic lipid, antibody, and where the cationic lipid is linked to the antibody by a heterobifunctional linker would have been obvious to one skilled in the art over the teachings of Kadouche and Singh. Kadouche provides the

teaching of coupling an antibody to a cationic type emulsion. Singh provides the teaching of a combination product comprising an active ingredient containing liposome linked to monoclonal antibodies using heterobifunctional reagents.

Regarding instant claim 2, the limitation of the product having a positive zeta charge would have been obvious to one skilled in the art over the cationic emulsion taught by Kadouche. A positive zeta charge is an intrinsic feature of a cationic emulsion and would be obvious to one skilled in the art.

Regarding instant claim 4, the limitation of the cationic lipids stearylamine or oleylamine would have been obvious to one skilled in the art over the stearylamine taught by Singh.

Regarding instant claim 5, the limitation of the emulsion comprising colloid particles having an oily core surrounded by an interfacial film would have been obvious to one skilled in the art over the liposomal preparation that comprises the cationic lipid stearylamine taught by Singh. One skilled in the art would know that the charge on an emulsion is conferred by the charge of the lipids used. Therefore, the use of a cationic lipid would lead to a positively charged emulsion.

Regarding instant claim 6, the limitation of the active principle in the emulsion would have been obvious to one skilled in the art over the monensin liposomes taught by Singh.

Regarding instant claim 7, the limitation of the polyclonal antibody would have been obvious to one skilled in the art over the polyclonal antibodies taught by Kadouche.

Regarding instant claim 8, the limitations of the monoclonal antibody would have been obvious to one skilled in the art over the monoclonal antibodies taught by Singh.

Regarding instant claim 9, the limitation of the antibody targeting an antigen on the surface of a pathological cell would have been obvious to one skilled in the art over the tumor specific antibodies taught by Singh.

Regarding instant claims 10-11, the limitations of the antibody targeting H-ferritin and AMB8LK antibody would have been obvious to one skilled in the art over the anti-ferritin monoclonal antibody AMB8LK taught by Kadouche.

Regarding instant claim 12, the limitation of the linker would have been obvious to one skilled in the art over the heterobifunctional reagent SPDP taught by Singh.

Regarding instant claims 13-15, the limitations of a method for producing the combination product would have been obvious to one skilled in the art over the heterobifunctional reagent SPDP that was used to introduce pyridyl disulphide groups into the monoclonal antibodies, as taught by Singh, and by the coupling of monoclonal antibodies to a liposome type vector or a cationic emulsion, as taught by Kadouche.

Conclusion

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615